Decision Memo for Autologous Blood Derived Products for Chronic Non-Healing Wounds (CAG-00190R2)

Decision Summary

CMS has determined that the evidence is inadequate to conclude that autologous platelet rich plasma (PRP) for the treatment of chronic non-healing cutaneous wounds, acute surgical wounds when the autologous PRP is applied directly to the closed incision, or dehiscent wounds improves health outcomes in the Medicare population. Therefore, CMS has determined that PRP is not reasonable and necessary for the treatment of these indications.

Consequently, CMS is issuing a non-coverage determination for acute surgical wounds when the autologous PRP is applied directly to the closed incision and for dehiscent wounds. CMS will maintain the current non-coverage for chronic, non-healing cutaneous wounds.

In accordance with section 310.1 of the National Coverage Determinations Manual, Medicare covers the routine costs in Federally sponsored or approved clinical trials assessing the efficacy of autologous PRP in treating chronic, non-healing cutaneous wounds.

The new NCD language can be found in Appendix C.

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Decision Memo

TO: Administrative File: CAG-00190R2 Autologous Blood-Derived Products for Chronic Non-Healing

Wounds (Second Reconsideration)

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SUBJECT: Coverage Decision Memorandum for Autologous Blood-Derived Products for Chronic Non-Healing

Wounds

DATE: March 19, 2008

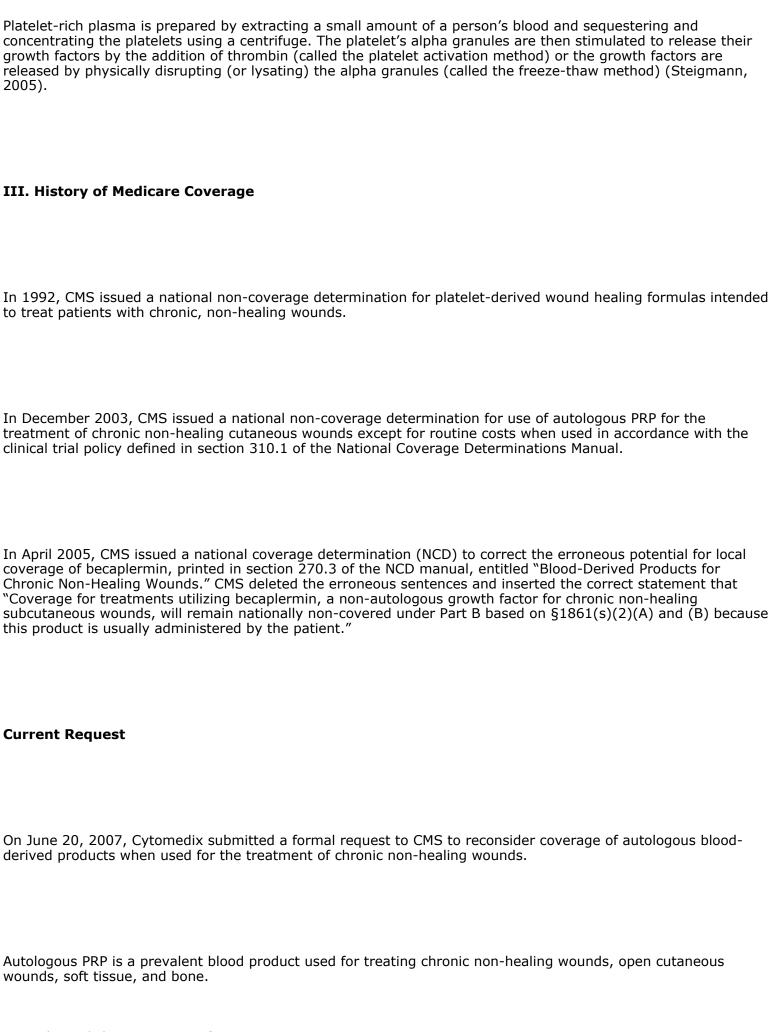
I. Decision

CMS has determined that the evidence is inadequate to conclude that autologous platelet rich plasma (PRP) for the treatment of chronic non-healing cutaneous wounds, acute surgical wounds when the autologous PRP is applied directly to the closed incision, or dehiscent wounds improves health outcomes in the Medicare population. Therefore, CMS has determined that PRP is not reasonable and necessary for the treatment of these indications.

Consequently, CMS is issuing a non-coverage determination for acute surgical wounds when the autologous PRP is applied directly to the closed incision and for dehiscent wounds. CMS will maintain the current non-coverage for chronic, non-healing cutaneous wounds.



A dehiscent wound is typically an incisional site that was closed at the end of surgery that has subsequently split open along the suture lines. Wound dehiscence is a potential complication that occurs as a result of poor wound healing.
Because normal wound healing involves many variables that interact in a dynamic and interactive manner, the reasons for abnormal wound healing are usually multi-factorial. Multiple physiologic and biochemical defects can lead to a failure to heal (Singer, 1999). The presence of co-morbid medical conditions increases this variability. For example, patients with diabetes suffer from vascular disease, which can limit the ability of wound healing-relevant cells and their growth factors to reach the wound area. Adding to the variability is the potential for each co-morbid condition to impact the normal wound healing process in a different manner. For example, the factors underlying the cause of a diabetic ulcer can, and usually are, different from the factors behind a pressure ulcer.
Given the multi-factorial manner of wound development, healing and failure to heal, with resultant different wound types, the management of chronic, cutaneous wounds is increasingly tailored to the specific type of wound. There are some treatments and strategies that are commonly used regardless of wound type such as debridement of dead tissue in the wound, maintaining a moist wound environment, infection control, and the reduction of recurring trauma to the wound. However, other procedures are customized by wound type; for example, intense regulation of the hemoglobin A1C level in a patient with a diabetic foot ulcer, or the restoration of arterial perfusion in a patient with an ulcer due to arterial insufficiency.
Background of the Procedure
Platelet releasates, including multiple growth factors, have been used for the treatment of wounds since the mid 1980s. (Driver, 2006) An example is becaplermin, which is an FDA-approved product that contains a single growth factor called platelet-derived growth factor (PDGF). Alternatively, autologous PRP provides a concentrated source of platelets and the numerous types of growth factors contained in their granules. Most notable are PDGF and transforming growth factor-ß (i.e., TGF-ß1 and TGF-ß2) but also include insulin-like growth factor, vascular endothelial growth factor, as well as other growth factors. (Steigmann, 2005)
Platelet-rich plasma is produced in an autologous or homologous manner. Autologous PRP is comprised of blood from the patient who will ultimately receive the PRP. Alternatively, homologous PRP is derived from blood from multiple donors.



Cytomedix submitted new evidence and requested CMS to re-evaluate the coverage of autologous PRP gel for the following open-cutaneous wounds, including chronic wounds:
 Wounds caused by an acute surgical incision or dehiscence. Full-thickness chronic wounds that have failed an adequate course of standard wound therapy.
On February 15, 2008, CMS received a letter from the submitter (Cytomedix) requesting that CMS revise the proposed decision memorandum to allow for coverage of autologous PRP "when used as a treatment of chronic diabetic foot ulcers." The letter also included a discussion about the use of a registry approach that would allow coverage of autologous PRP for treatment of chronic diabetic foot ulcers. The submitter explained that the use of a registry would permit CMS to continue to gather data that will help "develop the evidence base for improved treatment of diabetic foot ulcers."
Benefit Category
For an item or service to be covered by the Medicare program, among other things, it must meet one of the statutorily defined benefit categories outlined in the Social Security Act.
There is no specific Medicare benefit category for autologous blood-derived products for treatment of chronic no healing wounds. However, these services, at a minimum, fall within the benefit categories of physician's service ($\S1861(s)(1)$ of the Act) and "incident to" a physician's service ($\S1861(s)(2)(A)$ of the Act).
This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.
IV. Timeline of Recent Activities
June 25, CMS formally opened a national coverage analysis on Autologous Blood-Derived Products for Chronic Non-Healing Wounds.

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The initial public comment period opened.

July 25, 2007	The initial public comment period closed.
September 18, 2007	Cytomedix and wound care experts meeting at CMS.
October 15, 2007	Organogenesis meeting at CMS.
December 20, 2007	Proposed decision memorandum posted to CMS website. The public comment period for the proposed decision memorandum opened.
January 19, 2008	The public comment period for the proposed decision memorandum closed.
February	Cytomedix and wound care experts meeting at CMS

V. FDA Status

4, 2008

The AutoloGel™ System has been cleared by the FDA under Section 510(k) in a determination that the device is substantially equivalent (for the following listed indications) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976. The device "is intended to be used at point-of-care for the safe and rapid preparation of platelet-rich plasma (PRP) gel from a small sample of a patient's own blood. Under the supervision of a healthcare professional, the PRP gel produced by the AutoloGel™ System is suitable for exuding wounds, such as leg ulcers, pressure ulcers and for the management of mechanically- or surgically-debrided wounds."

FDA concluded, "Based on the clinical performance information, it can be concluded that AutoloGel is substantially equivalent to the marketed wound dressing IPM Wound Gel." (FDA 510(k) summary accessed at http://www.fda.gov/cber/510ksumm/k060007S.pdf accessed November 15, 2007.) The AutoloGel system is one example of systems that produce autologous PRP products.

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.
Methodological principles of study design that are used to assess the literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.
Public comment sometimes cites published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.
VII. Evidence
A. Introduction:
This DM focuses on the use of PRP in chronic, non-healing wounds; dehiscent wounds; or in acute wounds when PRP is applied directly upon the closed incision site (i.e., a cutaneous application). Consequently, the various subcutaneous uses of PRP (for example, during sinus or dental surgery, or for the treatment of chronic elbow tendinosis) are not addressed in this document. In addition, only autologous PRP is addressed and not PRP obtained from homologous sources.

A high quality of evidence is critical to determine whether an intervention improves the patient's health outcome. The highest quality of clinical evidence generally comes from prospective, controlled clinical trials. Hence, in this DM, CMS gives preference to results from controlled clinical trials that investigated autologous PRP. However, we also review other published evidence from observation studies as well as the professional opinions found in position statements or in review articles. We also consider public comments and evidence submitted for our review.

For chronic, non-healing wounds and for dehiscent wounds, CMS continues to use the primary outcome of interest that was used in the original NCD (CAG-00190N)-incidence of complete wound healing (also known as complete wound closure or one hundred percent re-epithelialization). A definitive outcome such as this allows for a confident generalization of the available evidence across studies, different types of studies, different types of wounds, and to the Medicare population. This is an important consideration given the variability of wound pathophysiology, the propensity for the use of an uncontrolled design in wound studies and since many patients in studies are less than 65 years of age.
Time to complete wound healing and incidence of wound infection are two additional outcomes that have been reported in the clinical literature. However, the incidence of complete wound closure is the most commonly used primary outcome.
For acute, surgical wounds that were closed upon completion of the surgical procedure, potential outcomes are incidence of dehiscence, severity of incisional pain and incidence of infection.
In June, 2006 the Food and Drug Administration (FDA) issued a guidance document regarding the clinical investigation of chronic cutaneous ulcer and burn wounds titled "Guidance for Industry. Chronic Cutaneous Ulcer and Burn Wounds—Developing Products for Treatment." The salient points from this document include:
• The guidance specifically addresses only three types of chronic cutaneous ulcers: venous stasis ulcer, diabetic foot ulcers, and pressure ulcers (FDA guidance, page 1).
FDA defines a chronic cutaneous ulcer as "a wound that has failed to proceed through an orderly and timely series of events to produce a durable structural, functional, and cosmetic closure" (FDA guidance, page 1). CMS considers this to be an important distinction from an acute wound, which has not had the opportunity to proceed through this orderly and timely series of events.

Regarding clinical trial design, randomization is "particularly important for reducing bias in wound indication trials because standard wound care procedures and baseline wound characteristics generally have a profound effect on outcome" (FDA guidance, page 5). FDA notes that standard care refers to generally accepted wound care procedures, which can vary from institution to institution and hence confound the assessment of the outcome (FDA guidance, page 8). To emphasize the importance of this point, the guidance devotes over three pages to the subject of standard care considerations (FDA guidance, pages 8-12). Of note, the guidance suggests the use of a "standard-of-care" or run-in phase, which is an initial stage of the trial where only standard-of-care treatment is administered, in order to minimize the variability in care and filter out those patients with significant wound healing simply due to improved compliance with standard-of-care treatment (FDA guidance, page 8).

Baseline wound characteristics can also impact the assessment of the outcome. Wounds differ in pathophysiology therefore "it is difficult to generalize results obtained from a trial conducted in subjects with one wound type to patients with another wound type" (FDA guidance, page 2). The guidance addresses the issues surrounding proper wound assessment and quantification (FDA guidance, pages 6-7).

Blinding of patients and investigators is advisable when feasible in order to reduce the chance for bias. If it is impractical or unethical to do so, at least a blinded assessment by a third-party evaluator should be incorporated into the trial design (FDA guidance, page 5).

The FDA guidance states that there are generally two broad categories of endpoints to demonstrate the efficacy of wound treatment products for regulatory approval: improved wound healing and improved wound care. Examples of specific endpoints to demonstrate improved wound healing include incidence of complete wound closure, accelerated wound closure, facilitation of surgical wound closure, and quality of healing (cosmesis and function). Examples of specific endpoints to show improved wound care include treatment of wound infection, debridement, and wound pain control (FDA guidance, pages 12-15).

CMS recognizes that products such as graftskin and becaplermin were required to conduct controlled clinical trials in order to obtain FDA approval or marketing clearance for the indication of improved wound healing. This is in contrast to the reduced regulatory barrier for the indication of wound management.

B. Discussion of evidence reviewed

1. Questions:

The development of an assessment in support of Medicare coverage decisions is based on the same general	
question for almost all requests: "Is the evidence sufficient to conclude that the application of the technolog	У
under study will improve health outcomes for Medicare patients?" For this NCD, the questions of interest are	::

Is the evidence sufficient to conclude that the use of autologous PRP for chronic, non-healing wounds, compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population?

Is the evidence sufficient to conclude that the use of autologous PRP for acute surgical wounds, compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population when PRP is applied directly to the closed incision?

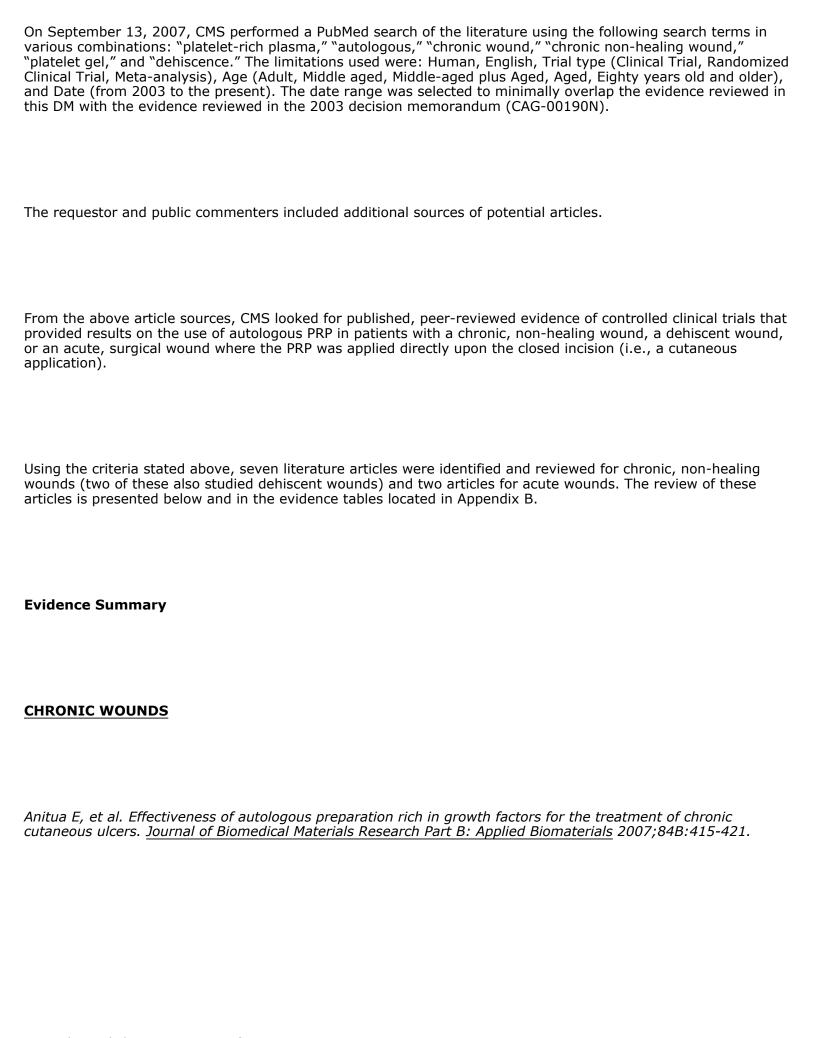
Is the evidence sufficient to conclude that the use of autologous PRP for dehiscent wounds, compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population?

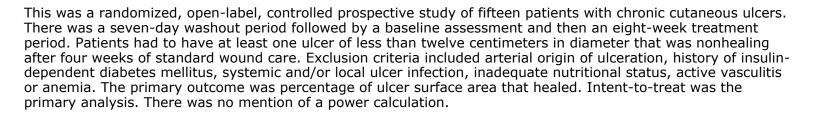
2. External technology assessments

On October 30, 2007, the Cochrane database, the NICE database, the Blue Cross/Blue Shield TEC database, and the Canadian Agency for Drugs and Technologies in Health database were searched using the terms "wound care," "platelet gel," and "platelet-rich plasma." No technology assessments were found.

AHRQ released a technology assessment dated March 8, 2005 titled "Usual Care in the Management of Chronic Wounds: A Review of the Recent Literature." This technology assessment presented a broad review of the products, techniques, and protocols used in wound management and did not address autologous PRP specifically except to state that growth factors "show promise but need further, more rigorous evaluation."

3. Internal technology assessments





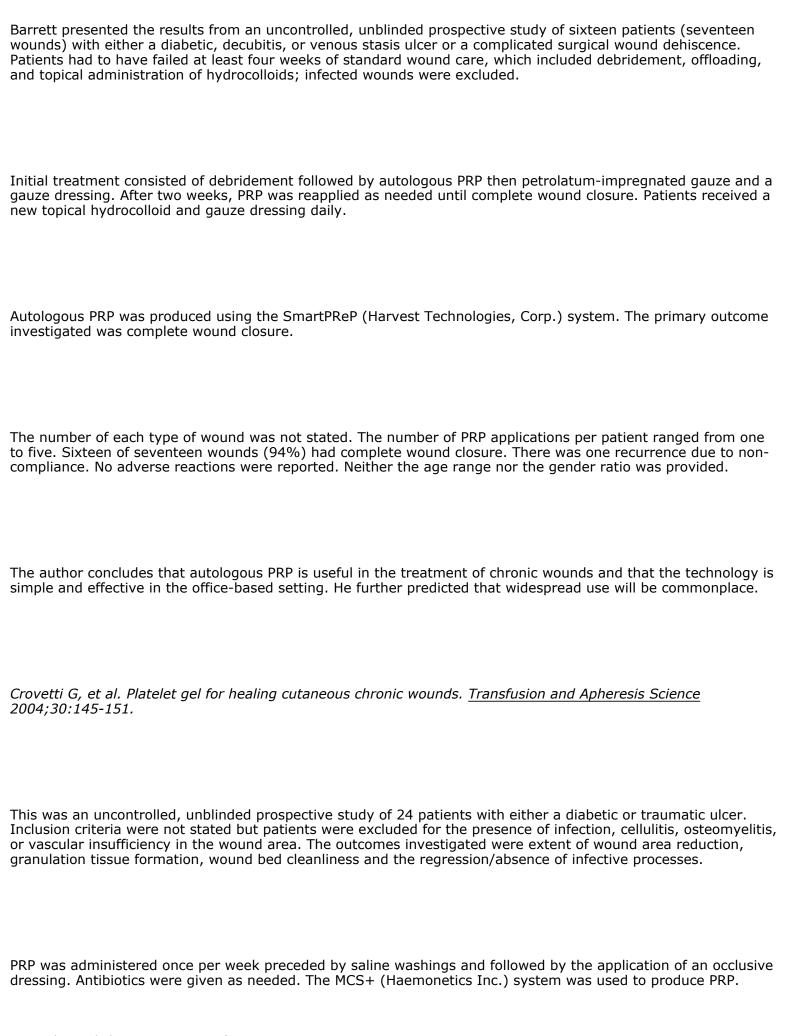
Initially both the PRP and the control groups received wound cleansing with normal saline and moist saline gauze dressings; debridement occurred if infection of the ulcer bed was suspected. The PRP group received a portion of the autologous PRP via injection into the margins of the ulcer and the remainder as a direct topical application to the ulcer bed; autologous PRP was administered once per week for eight weeks. Autologous PRP was produced using the PGRF System (BTI Biotechnology Institute, Vitoria-Gasteiz, Spain). The control group received debridement and saline cleansing once per week for eight weeks. Sterile moist saline gauze dressings were applied in both groups.

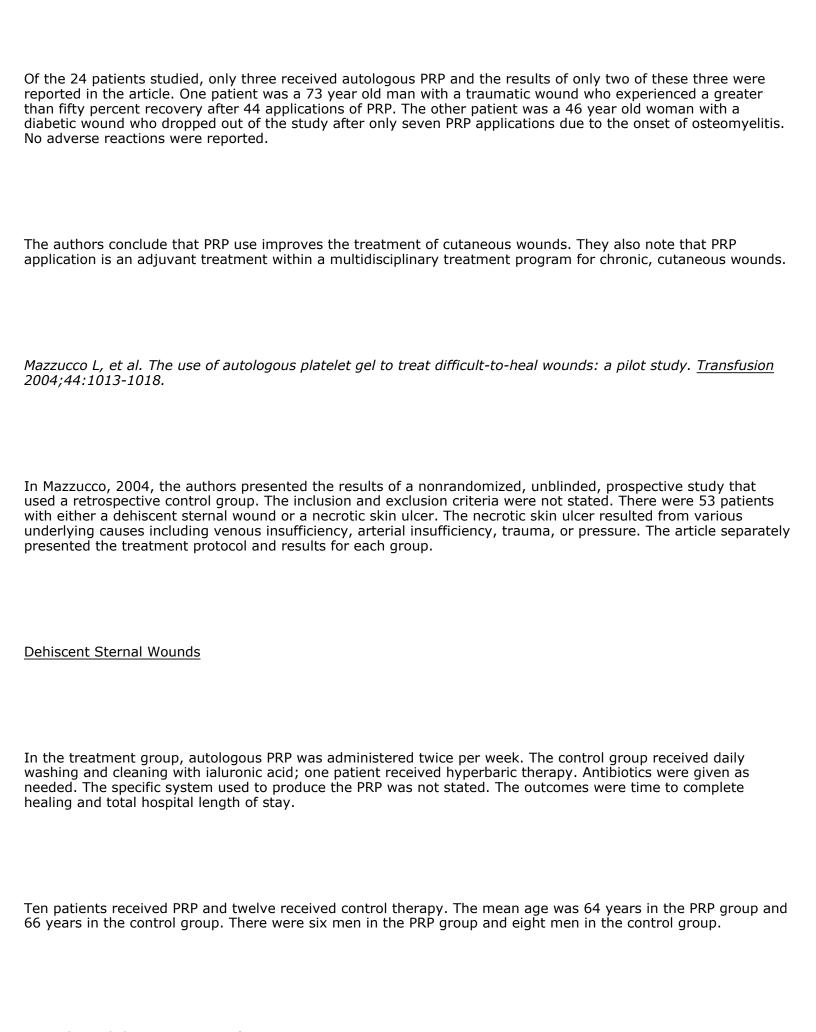
Fifteen patients were entered into the study; eight patients in the PRP group and seven patients in the control group. The authors did not report any statistically significant differences between the two groups. The mean age was 45 years for the PRP group and 61 years for the control group. The mean ulcer area was 5.5 cm² and 8.9 cm² for the PRP and control groups, respectively. Of the fifteen patients studied, three dropped-out of each group, which means that five patients in the PRP group and four patients in the control group completed the study. Sixty-four percent of the fourteen ulcers studied were of venous origin, 29% were of pressure origin and the remaining seven percent were reported as "other."

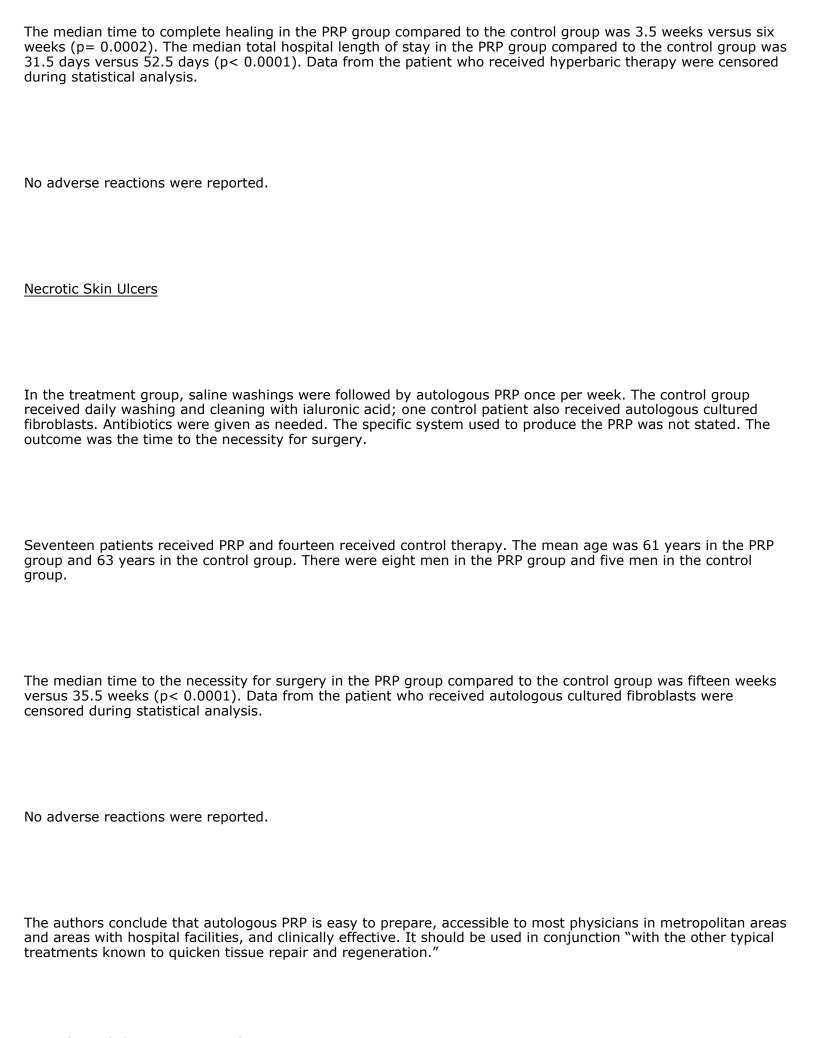
The mean percentage of surface healed at eight weeks was 72.94% and 21.48% in the PRP and control groups, respectively (p<0.05). Upon looking at the graft of the results, this statistically significant result appears to be based on a sample size of only nine (the originally planned intent-to-treat analysis would be based on a sample size of fifteen). Three patients experienced four adverse events (ulcer bed infection in one PRP patient and two control patients, and anemia in one patient).

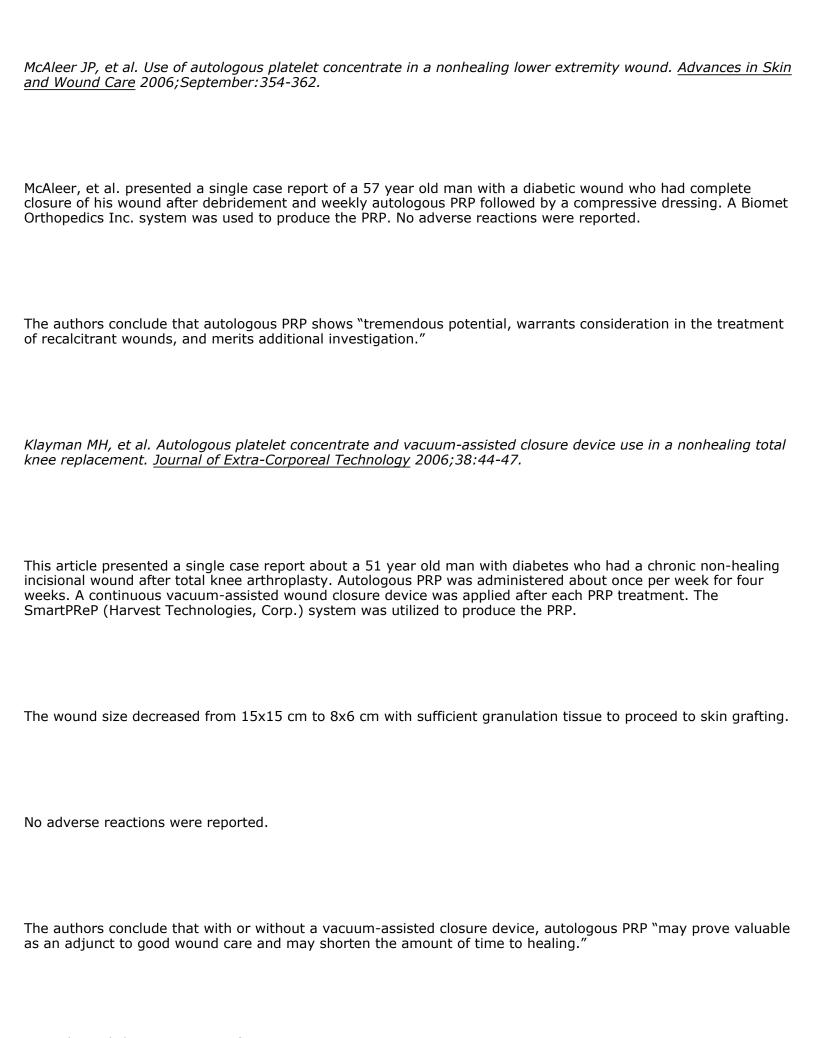
The authors acknowledge the small number of patients studied but conclude that the results "strongly support safety and effectiveness" of autologous PRP in patients with chronic ulcers and that additional "clinical trials with larger samples and larger end-points will be necessary to unequivocally establish the full potential" of autologous PRP.

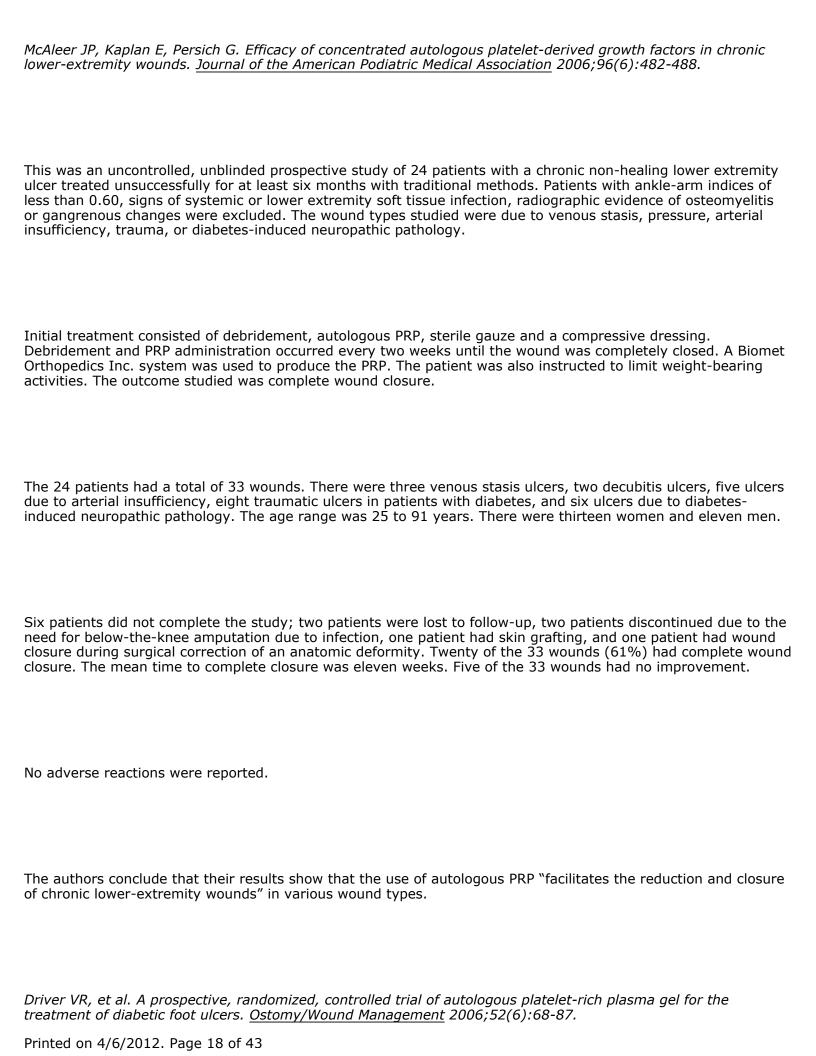
Barrett SL. A new approach to using growth factors in wound healing. Podiatry Today 2003;1:44-50.



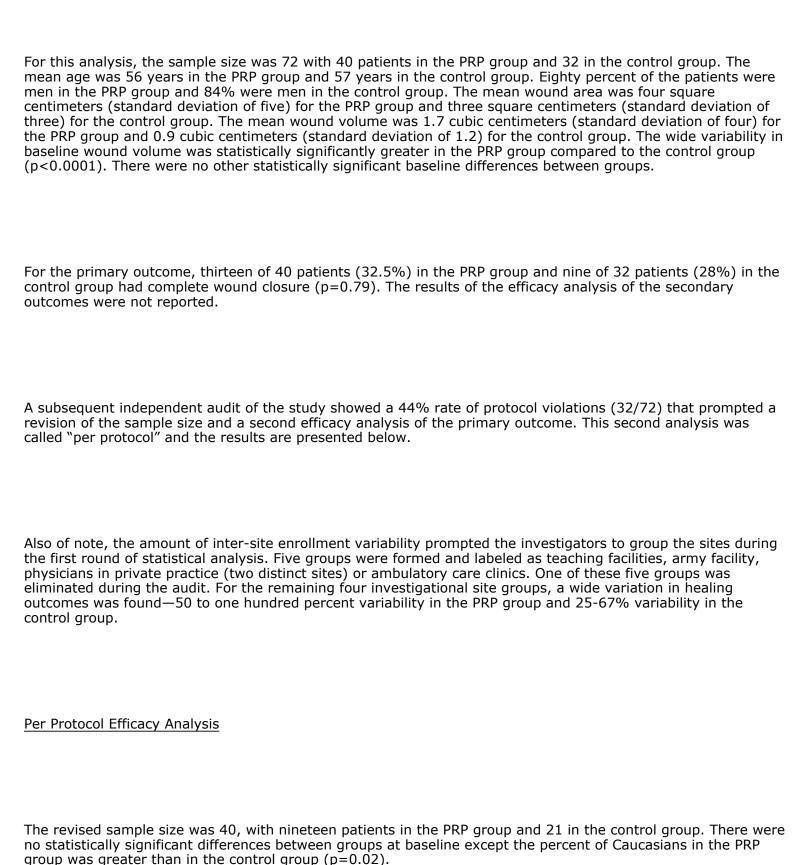


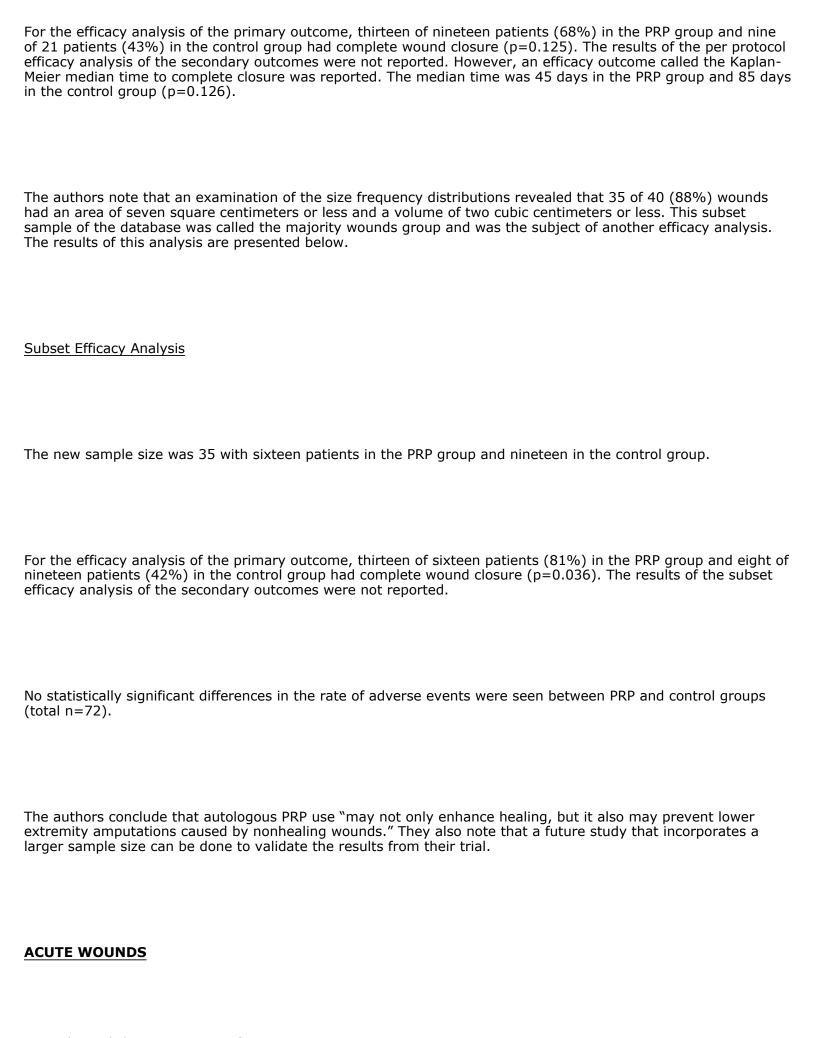














The low rate of infection overall precluded a subgroup analysis to determine the risk factors for infection.

The authors conclude that their results suggest the continued use of autologous PRP in patients with acute sternal wounds; however, its use "requires further prospective analysis to ascertain its benefit for improving outcomes." They also note that future studies should employ large sample sizes and measures of product quality. Lastly, consensus is needed regarding a uniform measure of infection and wound dehiscence, measures of product quality, and reporting of adverse events.

Hom DC, Linzie BM, Huang TC. The healing effects of autologous platelet gel on acute human skin wounds. Archives of Facial Plastic Surgery 2007;9:174-183.

Hom, et al. conducted a prospective, controlled, pilot study in healthy adult volunteers. Volunteers were excluded if there was a history of diabetes, keloid/scar formation, collagen vascular disease or bleeding disorder, or use of an anticoagulant or steroid during the month prior to enrollment.

Each volunteer received five full-thickness, punch biopsy wounds of four to six millimeters in diameter on each thigh. A punch wound and its corresponding punch wound on the other thigh were considered a "set." There were eight volunteers for a total of 80 wounds.

For each volunteer, each of the five sets of thigh punch wounds was assigned to one of five groups and one of two phases:

Phase 1

Group	PRP	Control
1	Applied on Day 0 + petrolatum ointment	Topical antibiotic

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Group	PRP	Control
2	Applied on Day 0	None

Phase 2

Group	PRP	Control
3	Applied on Days 0 & 7 + petrolatum ointment	Topical antibiotic
4	Applied on Days 0 & 7	None

Group 5 punch wounds were allowed to heal by secondary intention alone.

All wounds were covered with a semi-occlusive dressing.

The Magellan (Medtronic Inc.) system was used to produce autologous PRP.

Wound healing measurements were recorded for 42 days. Clinical assessment and blinded photographic assessment was used to study the percent wound closure over time, and the time required for complete wound closure.

The age range studied was 21 to 58 years and four of the eight volunteers were men.

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The results appear to be pooled across groups one through four for autologous PRP-treated and for control-treated groups, and then reported as PRP-treated versus control, despite the fact that each set of PRP-treated punch wounds received slightly different treatment. The text of the article gives an incomplete presentation of the percent wound closure over time results. Based on clinical assessment, for day seven the mean (SE) percent wound closure over time was 14% (1.1) for the PRP wounds and 7% (1.1) for the control wounds. For day fourteen, the mean (SE) percent wound closure over time was 73.9% (2.9) for the PRP wounds and 49.6% (3.6) for the control wounds. For day seventeen, the mean (SE) percent wound closure over time was 81.1% (2.5) for the PRP wounds and 57.2% (5.9) for the control wounds. The article text does not provide the results out to day 42 but a chart does provide this information.

In the chart, there is dispersion in the data between the PRP-treated and control groups from day seven through to day 31, with the PRP-treated group showing a greater mean percent closure compared to the control group. The widest dispersion between the groups occurs at days fourteen and seventeen. By day 35 both groups show 100% closure. The chart does not indicate the degree of variation around each data point. The presence or absence of statistical significance at each data point is also not indicated on the graph; however, in the text accompanying the chart the authors state "autologous platelet gel (APG)-treated sites had increased wound closure compared with the control sites over a 42-day period (P<.001)." Based on the data from digital photography, the authors state "the APG-treated sites had significantly increased wound closure compared to control sites over a 42-day period (P=.02, analysis of variance with repeated measures)."

For the outcome of time required for complete wound closure, on day 21, 63% of the PRP-treated wounds and 31% of the control wounds had complete closure. On day 24, 81% of the PRP-treated wounds and 44% of control wounds had complete closure. On day 28, 88% of the PRP-treated wounds and 56% of control wounds had complete closure. The average time to achieve complete closure was 29.75 days for the PRP-treated wounds and 35.38 days for the control wounds. None of these results achieved statistical significance.

No infections or serious adverse events were reported.

The authors conclude their results need to be confirmed by future studies. If its effectiveness is confirmed, autologous PRP use "could have a useful impact on the enhancement of postoperative dermal wound healing in surgical patients."

4. MedCAC

No MedCAC was convened for this topic.
5. Evidence-based guidelines
A summary clinical algorithm for a guideline by the Association for the Advancement of Wound Care was found during a search of the National Guideline Clearinghouse database. The algorithm, titled "Summary algorithm for venous ulcer care with annotations of available evidence" briefly notes the use of biologic dressings for wounds at least 30 days old as well as the use of platelet-derived growth factor. However, an evidence strength rating of "C" was assigned to each. This rating means that at least one of the following is lacking: results from a controlled trial, results of at least two case series or descriptive studies or a cohort study in humans, or expert opinion.
In 2006, the Wound Healing Society published evidence-based guidelines to demonstrate the best care of chronic wounds. The guidelines were presented by type of chronic wound (diabetic ulcers, venous ulcers, pressure ulcers, and arterial insufficiency ulcers). Only the venous ulcer guideline addressed a PRP-type of treatment and noted that this treatment has "yet to be shown to demonstrate sufficient statistically significant results or effectiveness to recommend" its use.
6. Professional Society Position Statements
An internet search failed to locate any professional society position statements exclusively concerning autologous PRP.
7. Public Comments
Initial comment period

During the initial 30-day public comment period, CMS received a total of 61 comments. Comments that were submitted via CMS coverage website may be viewed by using the following link: http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=208. The full summary of those comments can be found in our proposed decision memorandum on our coverage website.

Final comment period

CMS received a total of 22 public comments during the final 30-day public comment period. Two commenters were in favor of the proposed non-coverage decision, eighteen were opposed and favored some kind of coverage for PRP, and two expressed no clear indication for coverage. Comments that were submitted via the CMS coverage website may be viewed by using the following link: http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=208

Comments received via methods other than the CMS coverage website may be viewed by using the following link: http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=208

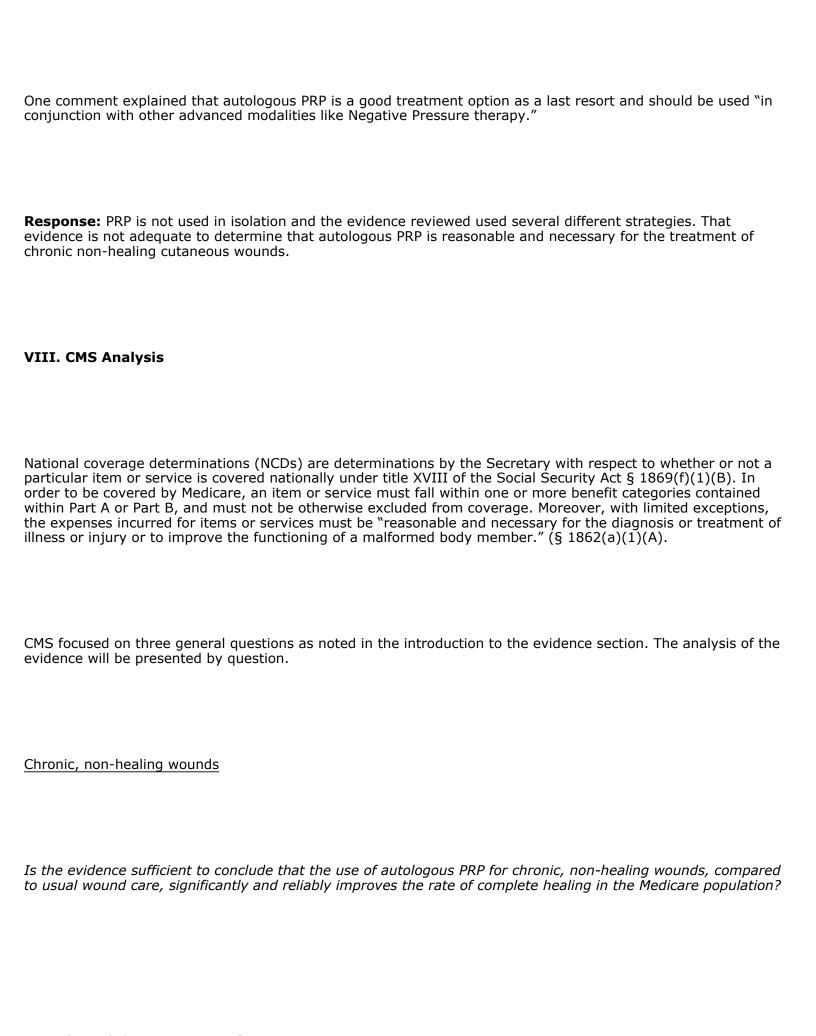
A. Comments with Evidence

CMS received a total of five comments that referred to evidence. Two of these comments were non-supportive of coverage; the remaining comments were supportive of coverage. Articles and information provided as evidence included studies and information already mentioned in the PDM; studies of PRP used in a manner unrelated to this DM; unpublished studies and information; review articles; a study that was published but not peer-reviewed; and studies of non-PRP products.

Response: Review articles do not provide additional information. Unpublished, and therefore, non-peer-reviewed, studies and information generally are accorded less weight than published and peer-reviewed material. Studies of the non-cutaneous use of PRP are not relevant to the cutaneous benefit of PRP. Please refer to Appendix A for additional information about CMS' evaluation of relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

One commenter submitted an article as evidence concerning a study that was not addressed in the PDM.
Response: This article has been addressed in the evidence and analysis sections of this memorandum.
B. Comments without Evidence
CMS received seventeen comments without evidence. Sixteen comments opposed the proposed non-coverage decision, favoring coverage, and one comment did not express a clear preference regarding coverage. CMS received comments from health care professionals, research organizations and the general public.
<u>Healthcare Professionals and Research Organizations</u> Of this category, CMS received thirteen comments from healthcare professionals. This category included physicians, hospitals, wound care specialists, perfusionists, and nurses.
Many commenters explained how the use of autologous PRP significantly improved wound healing in patients and explained that their patients reported no side effects from use of the therapy. Two commenters explained that they saw dramatic results in patients' wounds that did not respond to traditional therapy. One commenter suggested that the use of PRP is "very helpful in healing wounds with tunneling and undermining." One comment explained that "patients request PRP as a last resort before amputation of a limb and the results have been no lost (sic) of the limb." One commenter explained that the concentration level of PRP affects wound healing and explained that "if the concentration is not six times higher that (sic) base line there probably be no benefit to the wound." Another commenter was concerned about CMS using the standard of prospective randomized trials since "this standard was not used for multiple other wound care modalities either (Blue Sky Medical, Dermagraft, VAC, etc.)." One comment explained that autologous PRP gel "fits a need in a number of clinical areas that are currently underserved."
Response: While anecdotal reports are appreciated, less weight is given to anecdotal reports. These principles of evidence-based medicine are applied to all interventions that are reviewed for national coverage determinations (Appendix A).

One commenter suggested that using PRP gel would reduce wound treatment costs and shorten hospital length o stay for these patients.
Response: CMS does not consider costs in its national coverage determinations. Reduced length of stay was not a health outcome that CMS considered as part of this analysis.
General Public CMS received four comments from the general public. One comment explained that the use of PRP gel facilitates healing and reduces amputations. This commenter went on to say that CMS should "carve out from its non-coverage determination to those autologous platelet gel systems that (1) are FDA-approved, with indications for use in the treatment of chronic, non-healing wounds; and (2) are supported by randomized, blinded clinical trials having statistically significant results favoring the system's ability to improve the rate of wound closure in patients with chronic, non-healing wounds."
Response: Evidence does exist, but the evidence is not adequate to determine that autologous PRP is reasonable and necessary for the treatment of chronic non-healing cutaneous wounds. FDA status is addressed below.
One commenter indicated that it seemed inconsistent that the FDA "would provide clearance" of autologous PRP gel with a "specific indication for wound healing," but CMS would limit patient access to autologous PRP gel treatments in its proposed decision.
Response: When making coverage determinations, CMS evaluates whether an item or service is "reasonable and necessary." The FDA considers the safety and effectiveness of a product or device when making their clearance decisions.
CMS assesses relevant health outcomes, above and beyond the safety and effectiveness regulatory mandate of the FDA. Although a device must receive FDA approval or clearance for at least one indication to be eligible for Medicare coverage, except for a category B device under an investigational device exemption (IDE) clinical trial (60 FR 48417, September 19, 1995), FDA approval/clearance alone does not entitle that device to coverage. The device must fall under a Medicare benefit category and determined to be reasonable and necessary for the diagnosis or treatment of an illness or injury, or to improve the functioning of a malformed body member, to be covered by CMS.



The evidence base for chronic, non-healing wounds consisted of the results from eight articles. Three of these articles presented a controlled study; one was prospectively controlled, randomized, and double-blinded (Driver, 2006), one was prospectively controlled and unblinded (Anitua, 2007), and one was retrospectively controlled (Mazzucco, 2004). The remaining articles presented an uncontrolled study; either as a series of cases (Barrett, 2003; Crovetti, 2004; McAleer, 2006) or as a single case report (McAleer, 2006; Klayman, 2006).

The lack of randomization and blinding in uncontrolled study designs such as case reports and case series significantly impairs the ability to come to confident conclusions. Evidence generated from such study designs can suggest that a treatment may be useful but a controlled study design is needed to confirm a beneficial health outcome. Hence, the evidence found in Barrett, 2003; Crovetti, 2004; McAleer, 2006; McAleer, 2006; and Klayman, 2006 is interesting but not very useful for determining the health benefit of autologous PRP in patients with chronic, non-healing wounds.

The retrospectively controlled study employed by Mazzucco, et al. is an improvement over the uncontrolled study designs because it incorporates a comparator and permits a statistical analysis to determine if a statistically (as well as a clinically) significant difference in health outcome is achieved with the use of a particular treatment. However, this control group created from past health records has some potential sources of bias including a lack of randomization and blinding as well as the possibility that an outdated type of care was provided or the standard of care was provided in an inconsistent manner. These potential pitfalls must be taken into consideration when interpreting the results from Mazzucco, et al.

A prospectively controlled study design allows for the use of randomization and blinding, which can lead to the generation of robust evidence by limiting bias and confounding. This type of study design is noted prominently in the FDA guidance as presented in the introduction to the Evidence section of this DM. Of the eight articles investigating the use of autologous PRP in patients with a chronic, non-healing wound, only the articles by Driver, et al. and Anitua, et al. used a prospectively controlled study design. Unfortunately, the Driver study suffered from significant deficiencies during the conduct of the protocol that negatively impacted the data quality and statistical analysis. Consequently, a statistically significant result was not found until the authors narrowed down the evidence database and performed a previously unplanned statistical analysis. Hence, the results of this study can serve to generate hypotheses for future randomized, controlled trials but not to conclusively demonstrate the ability of autologous PRP to improve the rate of wound closure in patients with chronic, non-healing wounds. The results from the Anitua study suggest that PRP is useful for the treatment of chronic cutaneous ulcers compared to standard care but the sample size was very small. Even the study authors acknowledge that their results are preliminary and in need of confirmation via larger clinical trials.

Taken together, the eight articles had a total sample size of 184 patients. Sixty-five of these patients received various control therapies and 119 patients were given autologous PRP. The majority of these patients (49%) had a diabetic ulcer and the next largest group of patients had a sternal dehiscent wound (15%). These figures are only estimates, however, since one of the eight articles did not break out the sample size by wound type. Regardless, this is a very small number of patients investigated, especially given the variety of wound types that were studied. The differing pathophysiology and potential differing response to treatment of each type of wound could have negatively impacted the chance of this evidence to demonstrate a positive health outcome of autologous PRP in patients with chronic, non-healing wounds.

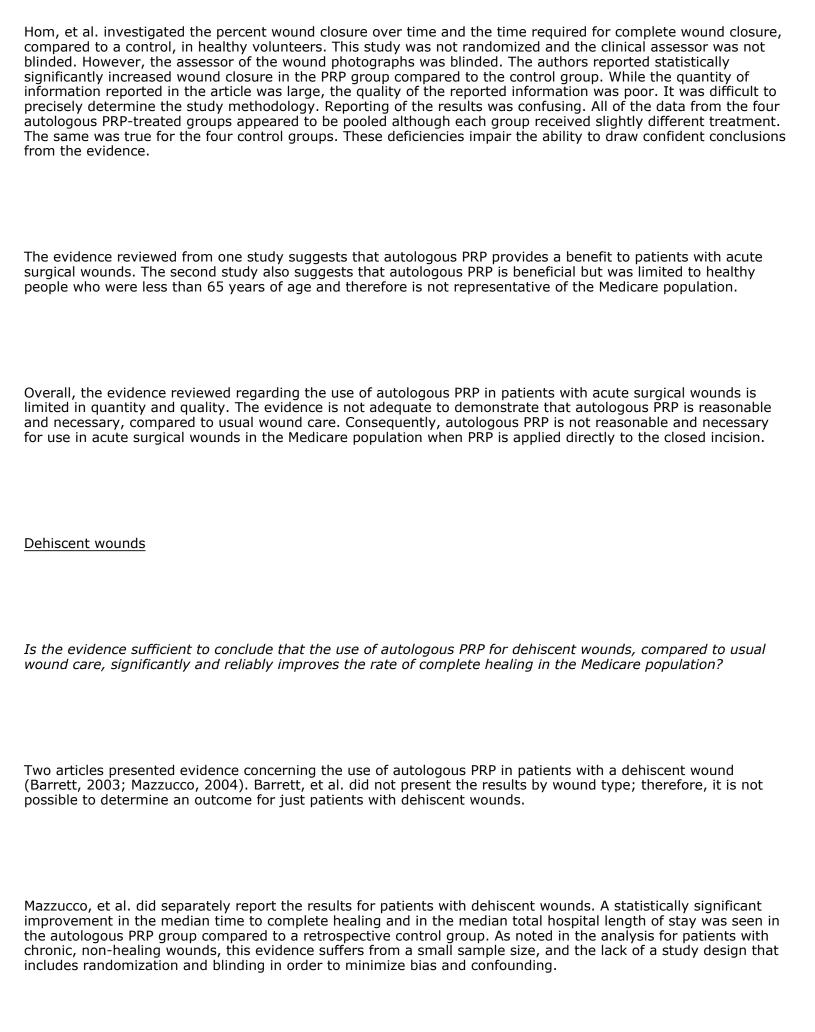
Another potential limiting factor on the ability of this evidence to demonstrate a positive health outcome in this patient population is the quality of PRP. The production of PRP involves a number of steps and ingredients at the "point-of-care." While a procedure is typically defined upfront, the consistency of application from patient to patient can be impacted by a number of factors including patient factors (e.g., blood platelet count), ingredient factors (e.g., thrombin quality; source of blood), and process factors (e.g., the type of centrifuge used, centrifugation time and RPMs; method of growth factor release). In his review of PRP from 2004, Marx notes that "not all currently marketed PRP devices are equal" and that studies "suggesting that there is no benefit from PRP can often be traced to poor-quality PRP produced by inadequate devices." CMS sought to minimize the impact of PRP quality by focusing only on autologous rather than homologous PRP; however, it was not possible to control for most of the potential limiting factors.

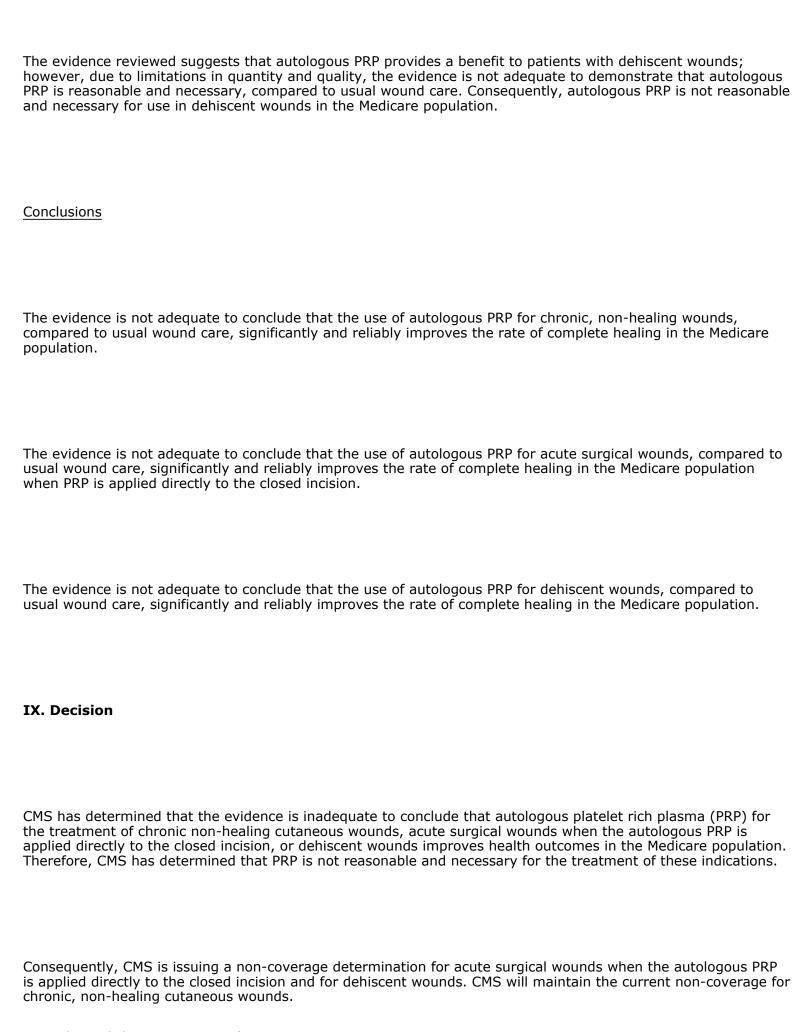
In the 2003 decision memorandum (CAG-00190N), CMS issued a national non-coverage determination for autologous PRP (except when used for chronic wounds in accordance with the clinical trial policy) based upon the absence of evidence of health benefits of the use of the treatment in this population. In the current DM, suggestive evidence is now available for review; however this evidence is significantly limited in quality and therefore inadequate.

Acute wounds

Is the evidence sufficient to conclude that the use of autologous PRP for acute surgical wounds, compared to usual wound care, significantly and reliably improves the rate of complete healing in the Medicare population when PRP is applied directly to the closed incision?

Two articles (Trowbridge, 2005; Hom, 2007) were reviewed to assess the use of autologous PRP in an acute wound. Trowbridge, et al. performed a prospective study in patients undergoing cardiac surgery that compared autologous PRP to a concurrent control group and a retrospective control group. The sample size was large; however, the study design suffered from a lack of randomization and blinding. Three different systems were used to produce the autologous PRP, which introduced a potential source of variability in the outcomes data. Despite these possible limitations, a statistically significant improvement was reported in the rate of superficial and in the rate of deep sternal wounds in the autologous PRP group compared to each control group.





In ac	cordance	with section	310.1 of the	National	Cover	age Detei	minations	Manual	, Medicare	covers the	routine
costs	in Federa	ally sponsore	ed or approved	d clinical	trials	assessing	the effica	cy of aut	tologous P	RP in treati	ng
chror	nic, non-h	nealing cutan	eous wounds.					-			

APPENDIX A: General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether
or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and
necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are
confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will
improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

• Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.

- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant
 outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to
 make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were
 assigned (intervention or control). This is important especially in subjective outcomes, such as pain or
 quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by
 either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.



A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.
If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.
Assessing the Relative Magnitude of Risks and Benefits
Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.
Appendix B: Evidence Tables [PDF, 153KB] Appendix C NCD Language
270.3 - Blood-Derived Products for Chronic Non-Healing Wounds - (Effective March 19, 2008)
(Rev.
A General

Wound healing is a dynamic, interactive process that involves multiple cells and proteins. There are three progressive stages of normal wound healing, and the typical wound healing duration is about 4 weeks. While cutaneous wounds are a disruption of the normal, anatomic structure and function of the skin, subcutaneous wounds involve tissue below the skin's surface. Wounds are categorized as either acute, in where the normal wound healing stages are not yet completed but it is presumed they will be, resulting in orderly and timely wound repair, or chronic, in where a wound has failed to progress through the normal wound healing stages and repair itself within a sufficient time period.
Platelet-rich plasma (PRP) is produced in an autologous or homologous manner. Autologous PRP is comprised of blood from the patient who will ultimately receive the PRP. Alternatively, homologous PRP is derived from blood from multiple donors.
Blood is donated by the patient and centrifuged to produce an autologous gel for treatment of chronic, non-healing cutaneous wounds that persists for 30 days or longer and fail to properly complete the healing process. Autologous blood derived products for chronic, non-healing wounds includes both: (1) platelet derived growth factor (PDGF) products (such as Procuren), and (2) PRP.
PRP is different from previous products in that it contains whole cells including white cells, red cells, plasma, platelets, fibrinogen, stem cells, macrophages, and fibroblasts. PRP is used by physicians in clinical settings in treating chronic, non-healing wounds, open, cutaneous wounds, soft tissue, and bone. Alternatively, PDGF does not contain cells and was previously marketed as a product to be used by patients at home.
In 1992, the Centers for Medicare & Medicaid Services (CMS) issued a national non-coverage determination for platelet-derived wound-healing formulas intended to treat patients with chronic, non-healing wounds. This decision was based on a lack of sufficient published data to determine safety and efficacy, and a Public Health Service technology assessment.
B. Nationally Covered Indications

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Not applicable.

C. Nationally Non-Covered Indications

- 1. Upon reconsideration, the clinical effectiveness of autologous PDGF products continues to not be adequately proven in scientific literature. As the evidence is insufficient to conclude that autologous PDGF in a platelet-poor plasma is reasonable and necessary, it remains non-covered for treatment of chronic, non-healing cutaneous wounds.
- 2. Additionally, the evidence is not adequate to determine that autologous platelet rich plasma (PRP) is reasonable and necessary for the treatment of chronic non-healing cutaneous wounds, acute surgical wounds when the autologous PRP is applied directly to the closed incision, or dehiscent wounds.
- 3. Coverage for treatments utilizing becaplermin, a non-autologous growth factor for chronic, non-healing subcutaneous wounds, will remain nationally non-covered under Part B based on §1861(s)(2)(A) and (B) of the Social Security Act because this product is usually administered by the patient.

D. Other

In accordance with section 310.1 of the National Coverage Determinations Manual, the routine costs in Federally sponsored or approved clinical trials assessing the efficacy of autologous PRP in treating chronic, non-healing cutaneous wounds are covered by Medicare.

(This NCD last reviewed March 2008.)

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